ANKYLOSING SPONDYLITIS*

BY

R. M. MASON

Department of Physical Medicine and Regional Rheumatism Centre, The London Hospital

It would seem appropriate to begin this paper by reflecting for a moment on the lady to whom, perhaps, venereologists owe everything, for is it not at least possible that had it not been for Venus herself the need for venereologists would hardly have existed? I am indebted to Dr. A. C. Young for his historical researches, for he reminds me that Anchises was a king who spent a night, doubtless many nights, with Venus. Unfortunately Zeus found out about it and threw a thunderbolt at him. Venus, however, so the story goes, was able to interpose her magic girdle; the thunderbolt was deflected onto his feet and Anchises, though alive, apparently never walked upright again. Venus was married to Vulcan; the Figure shews his kyphotic posture, the fact that

he has to be seated, and that his upper limbs are evidently spared but that he is careful to keep his heel off the ground.

After classical times a few years seem to have passed before much interest was shown in the clinical features of spondylitis. It is generally believed that Marie (1898) and his pupil Léri (1899), Strümpell (1897), and von Bechterew (1893) provided the first adequate descriptions of this disease, but O'Connell (1956) points out that many other descriptions preceded those published by these late 19th century writers who were unjustifiably rewarded with the eponymous nomenclature still occasionally used to-day. Bernard Connor, for instance, in 1695, described a skeleton found in a graveyard and noted fusion of the costovertebral joints and a dorsal kyphosis (Connor, 1695). Lyons (1831) described a

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FIGURE.—Vulcan the Smith at work. Note the kyphosis, that he has to remain seated and that he is careful to keep his heel off the ground.
(Courtesy of Dr. A. C. Young.)

man of 36 with arthritis of the spine leading to complete rigidity in 15 months. According to O'Connell, Lyons tried to arrange the admission of this patient to hospital in Dublin with a view to eventual autopsy, pointing out that Hunter had paid £100 for a skeleton with no history whatever whilst here was one fully documented which, with a little arrangement, could be had for nothing. The patient, a Manxman, evidently got wind of this and took himself off to the Isle of Man to die, leaving strict instructions to his relatives that after death his body was immediately to be cut up into small pieces. Be that as it may, a year later his bones found their way back to the Museum of the Royal College of Surgeons of Ireland, and they are described in the museum catalogue of that time. Brodie (1850), who first described what is now known as Reiter's disease, reported a patient seen in 1841 with pain and stiffness of the lumbar and dorsal spine, buttocks, and thighs, and arthritis of one knee, who also developed iritis.

But to skim a few more years, we find that increasing recognition of the clinical picture, especially in World War II and the post-war years, when most young men came under medical supervision as a result of National Service, has led to a clear characterization of ankylosing spondylitis. Hart, Robinson, Allchin, and MacLagan (1949), Hart (1954, 1955), and Baird (1955) in particular have presented us with a clear-cut clinical picture of an arthritis, always involving the sacro-iliac joints, often the spine, and less commonly the peripheral joints, affecting young men, with an average age at onset of 27 years, most commonly in the 15-24 decade and less frequently in the 25-34 and 35-44 decades, nearly 10 per cent. having a pre-pubertal onset (Hart, 1955; Mason, Murray, Oates, and Young, 1958).

The initial symptom in three-quarters of cases is low backache or stiffness, stiffness of the groins, thighs, or buttocks, worse in the early morning, often disturbing sleep, and relieved by moving about. Less commonly, the presenting symptom is in the dorsal region, chest, neck, or shoulders, and this is often when the disease has progressed silently for some years. For example, a golf professional was recently referred with "fibrositis" of the neck. Examination revealed a rigid lumbar and dorsal spine with some limitation of cervical movements. His ankylosing spondylitis had only revealed itself when the cervical spine had become affected and he was no longer able to keep his head down while playing golf. In about 10 per cent. of cases the onset is in the periphery, almost always in the lower limbs, with an arthritis of the ankles, heels, or feet.

Ankylosing spondylitis should always be considered in the differential diagnosis of an inflam-

matory arthritis of the knees, and x rays of the sacro-iliac joints may reveal sacro-iliitis. Clinical examination of the patient may show limited movements of the lumbar spine, often first affecting lateral flexion. Important additional physical signs include reduced respiratory excursion due to involvement of the costo-vertebral joints and tenderness of bony prominences, especially of the ischium, greater trochanters, or symphysis pubis. Forced movements of the sacro-iliac joints producing pain is, in our experience and that of others (Newton, 1957), a most reliable physical sign. The incidence of iritis, or more precisely unilateral non-granulomatous anterior uveitis, is variously estimated. Hart (1955) found an overall incidence of 13.5 per cent. in his series rising to 40 per cent. in those with a history of 15 years or more and aged over 45 years. Wilkinson and Bywaters (1958) had an overall incidence of 25 per cent., while 36 per cent. of patients with peripheral joint symptoms also had iritis. This compares with a much lower incidence of iritis associated with rheumatoid arthritis (3.5 per cent.: Duthie, 1955) and indeed it is probably true that there is no significant association between iritis and rheumatoid arthritis (Stanworth and Sharp, 1956). It seems likely that the suggestion of an association with rheumatoid arthritis is due either to misdiagnosis or to the concept that rheumatoid arthritis and ankylosing spondylitis are one and the same disease. It is curious that conjunctivitis, not iritis, is associated with Reiter's syndrome, at least in the early accounts of this disease. However, Paronen (1948) had a 6.6 per cent. incidence in his Finnish series, Zewi (1947) 10 per cent., and Ford (1953) a 30 per cent. incidence, although (as Stanworth and Sharp point out) Ford's series was selected inasmuch as all his patients were suffering from arthritis of 5 years' or more duration. Iritis may be the presenting symptom, or at least the symptom which first draws attention to the disease (Teschendorf, 1933; Chan and Sun, 1951; Birkbeck, Buckler, Mason, and Tegner, 1951; Romanus, 1953). Peptic ulceration also appears to be more common than in the normal population—some 10 per cent. of patients developing clinical or radiological evidence. This complication has a very serious effect on therapy. That ankylosing spondylitis may also be familial is now well recognized. Hersch, Stecher, Solomon, Wolpaw, and Hauser (1950) studied the incidence in fifty families and showed that inheritance is due to an autosomal dominant factor with 70 per cent. penetrance in males and 10 per cent. in females; Graham and Uchida (1957) added that when the affected female is the mother penetrance may be increased to nearly 100 per cent. One family, which I have previously briefly reported (Mason, 1951),

illustrates the kind of familial history one may encounter. The daughter, who presented first, had typical ankylosing spondylitis; her brother had backache, and on investigation was also found to have the disease. Both these children admitted that the father had had backache but, being a fairly tough character, he had never really complained about it. X-ray examination of his spine showed advanced changes of ankylosing spondylitis.

Recently, a man attended the out-patient department at the London Hospital with unilateral sacro-iliitis, the nature of which was obscure. We then discovered that his brother had also attended the hospital some 2 years previously, and examination of his x rays showed that he had bilateral sacro-iliitis. It was clear, therefore, that the brother with a unilateral sacro-iliitis was almost certainly suffering from ankylosing spondylitis.

Finally, x-ray evidence of bilateral sacro-iliitis is mandatory to confirm the diagnosis. I do not propose to discuss in detail the radiological signs, since they have been well described not only by Grainger (1957) but by Golding (1936), Hart (1955), and Forestier and Deslous-Paoli (1957).

Characterization of the disease on the basis of this picture removed from medicine one of the most common causes of diagnostic error, and the old saying that every spondylitic had a story to tell, a story of multiple diagnosis, of multiple palliative therapy, psychiatry, osteopathy, and so on, is no longer true; indeed, in the R.A.M.C. series, over half the cases were diagnosed within 2 years of the first symptom (Baird, 1955). If we add to this the widely-held belief that radiotherapy is effective, we can sum up the whole story in this equation:

Bilateral sacro-iliitis = Ankylosing spondylitis
Ankylosing spondylitis = Radiotherapy
Radiotherapy = Cure.

Such a very simple view deserves the most careful examination.

Relationship to Other Diseases

Rheumatoid Arthritis. — Full agreement on this subject has not yet been achieved. Short, Bauer, and Reynolds (1957), from the Massachusetts General Hospital in Boston, include ankylosing spondylitis in their series of patients with rheumatoid arthritis. Collins (1949) says that he can see no pathological distinction between the two diseases, although Van Swaay (1950, 1951) and Cruickshank (1951) distinguish them on pathological grounds. The cartilaginous proliferation which can be seen in ankylosing

spondylitis does not occur in rheumatoid arthritis, there is a tendency to haemorrhage into affected tissues, and the marked endarteritis obliterans with frequent bony ankylosis are all distinguishing features. Perhaps the regularly negative serology of ankylosing spondylitis, found not only by ourselves (Mason and others, 1958) but by many other workers (Svartz and Schlossmann, 1950; Ball, 1952; Brown, Badin, and McEwen, 1954; Wilkinson and Bywaters, 1958), is the most important and decisive distinguishing feature. But sacro-iliitis can occur in rheumatoid arthritis. We have observed unequivocal bilateral sacro-iliitis in some 10 per cent. of our cases of rheumatoid arthritis, the films being read blind (Mason and others, 1958). Moreover, the peripheral joint changes of ankylosing spondylitis may be very similar both clinically and radiologically, *e.g.* the periostitis, the heel erosions, and the simple plantar spurs. These are all non-specific changes, although plantar periostitis does not seem to occur in rheumatoid arthritis and may perhaps be specific for Reiter's disease. The peripheral joint changes of rheumatoid arthritis may give a radiological picture indistinguishable from that of Reiter's disease. Spondylitis can also occur in rheumatoid arthritis. Sharp (1957) and Sharp, Purser, and Lawrence (1958) have very clearly described the differences. In rheumatoid arthritis with spinal involvement, it is the cervical spine alone which is involved, but the cervical spine is never the only site of ankylosing spondylitis. Complete rigidity of the spine is very rare in rheumatoid arthritis and the radiological appearances are quite different—there is multiple disk narrowing, it involves the disks above C.4, there is little or no osteophytosis, there are erosions of the vertebral plates, vertebral subluxation of more than mild degree occurs, and there is involvement of the atlanto-axial joint. Erosion of the apophyseal joints also occurs. In juvenile rheumatoid arthritis, involvement of the cervical spine is common and is characterized by atrophy or hypoplasia of the vertebrae with ankylosis of the apophyseal joints.

Rheumatic Fever. — This can also, though rarely, cause a chronic arthritis (Jaccoud, 1869; Poynton and Pain, 1913; Bywaters, 1950). Thomas (1955) characterized this syndrome as one of recurrent polyarthritic episodes, rheumatic valvular disease of the heart, and atypical spondylitis with peripheral joint changes. Sharp (1957) also described nine cases. The condition can be distinguished from ankylosing spondylitis by the ligamentous laxity associated with abnormal mobility in the peripheral joints and, in the spine, by the lack of severe deformity and by the usually normal chest expansion. The sacro-iliac joints

are abnormal in about half the patients but the changes are not distinct from those of ankylosing spondylitis, although in the spine itself the antero-posterior narrowing of the vertebral bodies and the narrowing of multiple disks, with osteophytosis, hypoplasia of the vertebrae, and ankylosis of the apophyseal joints, are characteristic of rheumatic fever.

Psoriasis.—Many workers have commented on the association between psoriasis and ankylosing spondylitis (Sherman, 1952; Sterne and Schneider, 1953; Fletcher and Rose, 1955). Wright (1956) found three out of 34 cases of psoriatic arthritis to have ankylosing spondylitis, and Sharp (1957) also found a painful limitation of spinal movements in three-quarters of his patients, although he remarked on the fact that the sacro-iliac joints were often normal in patients with clinical spinal disease in this condition. The nails of the psoriatic may, of course, look rather similar to those seen in cases of keratoderma.

Ulcerative Colitis.—Steinberg and Storey (1957) recently described six cases of ankylosing spondylitis associated with chronic non-specific inflammatory disease of the intestines. Bywaters and Ansell (1958) found sacro-iliitis in six of 37 cases of ulcerative colitis with arthritis, the radiological appearances being indistinguishable from ankylosing spondylitis. The association with dysentery is, of course, well established (Paronen, 1948; Reiter, 1916; Fiessinger and Leroy, 1916).

Reiter's Disease.—It is also clear that sacro-iliitis and, indeed, spondylitis (apparently ankylosing) is a fairly common sequel to Reiter's disease. Ford (1953) found four cases of ankylosing spondylitis in his 21 cases of Reiter's disease and we (Mason and others, 1958; Oates, 1958) found that, in over 30 per cent. of our cases of Reiter's disease, there was unequivocal evidence of bilateral sacro-iliitis. In those cases with a history of six years or more, the number rose to 54 per cent. Others have commented on this before us (Marche, 1950; Sharp, 1957; Thompson, 1957). We have not been able to distinguish any qualitative difference in the sacro-iliac joints, but severe erosions, marked sclerosis, and particularly ankylosis only seem to occur in Reiter's disease and ankylosing spondylitis and we have not ourselves seen it in rheumatoid arthritis. However, Sharp (1957) states that he has observed fusion of the sacro-iliac joints in rheumatoid arthritis also. We have mostly been impressed with the difference in the time of development, sacro-iliitis occurring early in ankylosing spondylitis, and late in Reiter's disease. Sacro-iliitis is also an

occasional feature of brucellosis and Marfan's syndrome. It is clear, therefore, that the naïve belief that Bilateral Sacro-iliitis=Ankylosing Spondylitis does not stand up to examination, certainly if we accept the concept that there is such a disease entity as ankylosing spondylitis.

Treatment

Radiotherapy.—Turning to the second step of this simple equation, how does this stand up to examination? It is a strange thing that this form of therapy, the possible dangers of which have recently been recognized, should be so readily accepted as being effective. If one examines the evidence on which this belief is founded, one is startled to find more evidence of opinion than of data on which to base such an opinion. Desmarais (1953) carried out one of the few controlled studies of the value of radiotherapy in this disease. He limited his follow-up to 3 months, but he did find symptomatic relief in some 90 per cent. of the patients given a dose of 1000-2000 r. Nevertheless, he noted that 44 per cent. of his controls were also relieved. His numbers were small and no treatment group exceeded twenty cases. In addition he found x-ray evidence of progression of the disease in some of the cases who had obtained symptomatic relief. Sharp and Easson (1954) draw a clear distinction between what they call typical and atypical spondylitis in the response to radiotherapy. They found a significant symptomatic response only in the typical group, but they too drew attention to the tendency of the irradiated patients to relapse. Hart (1958), whilst claiming that deep x ray therapy commonly produced clinical improvement, which might last for months or years, also said that it was debatable whether it altered the natural course of the disease—"Our own feeling is", he says, "that it does not." Wilkinson and Bywaters (1958), in their large series, were likewise unimpressed by the real value of radiotherapy, and found a high relapse rate on adequate follow-up. We must weigh against this the risk of irradiation of the spine—an area containing active bone marrow to say nothing of the genital organs, especially of the female, in the neighbourhood. Brown and Abbatt (1955) and Abbatt and Lea (1956) have made a very careful statistical study of the incidence of leukaemia in men irradiated for ankylosing spondylitis, and it seems clear that leukaemia is significantly more frequent in patients who have received radiotherapy. In one group the percentage reached twenty times that to be expected, and it seems that an incidence of about 0.5 per cent. of leukaemia must be expected in patients so treated. Whilst this can hardly be said to be a high incidence

there would appear to be no doubt that by submitting our patients to radiotherapy we are exposing them to a real risk of developing leukaemia—a fatal complication. This calls for at least fairly convincing data that radiotherapy is more than palliative treatment.

Alternatives to Radiotherapy.—Our own experience in our Department at the London Hospital has been that adequate palliative control of the disease can usually be obtained with phenylbutazone (Butazolidin) in small doses of 200 mg. a day, often with as little as 100 mg. a day, combined with mobilizing physiotherapy, supervision of posture, control of activity (mostly encouragement of activity except in the very active phases), and control of acute exacerbations, if necessary, by steroids. These measures reduce the number of cases “needing” radiotherapy to the few resistant cases, perhaps with active peptic ulceration, in which surgery is for one reason or another not practicable, and I believe that even for this group radiotherapy rarely offers a solution.

Genital Infection.—We have shown (Mason and others, 1958) that a significantly high proportion of patients with typical ankylosing spondylitis have evidence of chronic prostatitis, and, having carefully examined the data, we conclude that this prostatitis is a feature of the disease and not of some other factors such as age distribution. Our figures are very similar to those of Romanus (1953), who studied 117 cases of ankylosing spondylitis but without controls. Nor, indeed, is this a new idea. Running through the whole literature of ankylosing spondylitis is this recurrent theme of genital infection—“gonococcal”, of course, before non-specific urethritis was recognized (Marie, 1898; Forestier, 1935, 1939; Volhard, 1938, 1943; and many others). Olhagen, Domeij, Giertz, and Romanus (1957) and Romanus (1953) found that some 33 per cent. of their patients with ankylosing spondylitis gave a previous history of gonorrhoea. This work was done in Sweden, however, and does not accord with our results in Whitechapel, where we have found a previous history of urethritis in only 9 per cent. of our ankylosing spondylitics—an incidence comparable with that seen in our rheumatoid group (5 per cent.) whilst 46 per cent. of the patients with Reiter’s disease showed an incidence of previous urethritis (Mason and others, 1958).

Attention has already been drawn to the development of spondylitis in Reiter’s disease. How should these findings influence our treatment? Should we submit all our spondylitic patients to a determined attempt to eradicate “infection” from the genito-urinary tract? We should be very careful here. After all we have no evidence that genital infection *per se*

is the *cause* of typical ankylosing spondylitis. Indeed we know that in nearly 10 per cent. of these patients the onset of the disease occurs before puberty. I am also impressed with the familial features of the disease—a familial incidence which does not seem to occur in Reiter’s disease. And there are other differences to which I have already alluded—in particular the difference in the time of development of sacro-iliitis, early in ankylosing spondylitis with a silent prostatitis and late in Reiter’s disease with a florid urethritis.

There are at least two fundamental difficulties here:

- (1) The complete failure to identify the organism responsible for Reiter’s disease. No doubt this is a virus for I do not think that the P.P.L.O. can any longer be seriously suspected, despite the pioneer work of Dienes and Weinburger (1951) over many years. There is also our complete lack of knowledge of the aetiology of ankylosing spondylitis.
- (2) The second difficulty is perhaps a philosophic one, for, as Bywaters (1958) recently pointed out, we run into difficulty the moment we begin to think of a disease as a real thing, in the sense, as he says, that a giraffe or a hippopotamus is a real entity. Diseases are no more than reaction patterns to a variety of stimuli. Now if, with our inadequate, sketchy knowledge, one feels that the reaction pattern in an individual case is characteristic of Reiter’s disease then I think that eradication of the genital infection should be attempted, although I should be glad to learn that this is possible and that there is evidence that by doing so one can influence the natural course of the disease. If, on the other hand, the reaction pattern is that which we have come to regard as typical of ankylosing spondylitis, then I doubt whether the presence of prostatitis is more than of theoretical interest. However, on this question controlled data are needed. It may well be reasonable to argue on the other hand that every effort should be made in fresh cases of urethritis to eradicate the resulting prostatitis in an endeavour to reduce the number of cases of spondylitis, and perhaps uveitis, in later years. What does seem absolutely clear is the tremendous importance of identifying the “virus” of Reiter’s disease. This would indeed represent a major advance in our knowledge and would put us into the position where some at least of these speculations could be answered.

Summary

The history of the development of our present concept of ankylosing spondylitis is briefly reviewed and the present day characterization of the disease described.

The various conditions which can give rise to sacro-iliitis are considered and the place of radio-therapy in the treatment of ankylosing spondylitis is critically considered.

The role of genital infection in ankylosing spondylitis, especially in relation to Reiter's disease, is discussed.

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